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INVITED RESEARCH HIGHLIGHT

Prostate Cancer

Long-term survival of participants in the prostate cancer prevention trial

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The Prostate Cancer Prevention Trial (PCPT) is a seminal study in the field of urology. More than 10 years after its initial publication, updated data from this trial continue to shape our understanding of prostate cancer. Among the major findings from the PCPT has been the demonstration that prostate cancer is common in men with prostate-specific antigen (PSA) once thought to be in the normal range,[1] finasteride prevents the development of benign prostatic hypertrophy,[2] it increases the sensitivity of PSA[3] and digital rectal examination.[4] Furthermore the PCPT helped to establish the link between erectile dysfunction and cardiovascular disease,[5] and perhaps most importantly finasteride demonstrated a 25% relative risk reduction in the diagnosis of prostate cancer compared with placebo.[6]

However, enthusiasm for the use of finasteride as a chemopreventive agent has been tempered by the finding of an increase in the incidence of high-grade prostate cancer detected by biopsy, which has led to an ongoing debate over the past decade. Briefly, the PCPT randomized 18,880 patients to placebo versus finasteride for 7 years, with all patients receiving yearly digital rectal exam and PSA screening (adjusted for finasteride).[6] Finasteride is a type II 5a-reductase inhibitor (5ARI) which inhibits the conversion of testosterone to the more potent dihydrotestosterone and results in a reduction in the volume of the prostate. Finasteride is currently Food and Drug Administration (FDA) approved for the treatment of benign prostatic hyperplasia. At the end of the study all men in whom prostate cancer had not been diagnosed were offered end-of-study prostate biopsies (regardless of whether there was a PSA increase or exam abnormality).

In the recent report on the PCPT in the New England Journal[7], similar to earlier reports, the authors note significant overall reduction in the diagnosis of biopsy proven prostate cancer in the group treated with finasteride with follow-up up to 18 years (10.5% *vs* 14.9%; risk ratio (RR) 0.70; 95% confidence interval (CI) 0.65–0.76; $P < 0.001$). Important to note, the reductions in the relative risk of prostate cancer were found entirely due to reductions of Gleason 6 or less (low-grade cancers) (RR = 0.57; 95% CI 0.52–0.63; $P < 0.001$), however, there was a statistically significant increase in the risk of Gleason 7–10 grade cancers; 333 (3.5%) in the finasteride group and 286 (3.0%) in the placebo group (RR = 1.17; 95% CI 1.0–1.37; $P = 0.05$). In this report the authors focus much of their attention on the long-term survival of men in both arms of the trial in order to better evaluate the importance of the Gleason 7–10 cancers, referred to in the study as 'high-grade' cancers. After up to 18 years of follow-up, no difference was noted in overall survival between arms. Furthermore, for the 2401 men who were diagnosed with prostate cancer, there were no significance differences in the rate of death after the date of diagnosis either in unadjusted (hazard ratio (HR) =1.01; 95% CI 0.85–1.2; $P = 0.9$) or in models adjusted for cancer grade, age, race and family history of prostate cancer (HR = 0.93; 95% CI 0.78–1.12; $P = 0.45$).

The cause for the increased risk of high-grade cancers as detected by biopsy in the finasteride arm of the PCPT is unclear; it is most commonly thought to be due to either a 'detection bias' or an induction of higher grade cancers. Supporters of the 'detection bias' theory argue that finasteride results in a decrease in prostate size by reducing the amount of benign prostatic stroma without a direct influence on the cancer and thereby altering the ratio of cancer to benign tissue. Thus, any biopsy is more likely to detect a given focus of cancer. Alternatively, some have suggested that the relative androgen depleted environment induced by finasteride may directly promote aggressive tumor growth or dedifferentiation. While the recent PCPT study does not directly resolve this issue, the authors point out that with more than 15 years of follow-up there is no evidence that finasteride use results in more lethal tumors.[7]

A 43% relative risk reduction in low-grade cancers for men in the finasteride group documented in the recent PCPT report is of interest. In 2012 (in the United States), prostate cancer was newly diagnosed in more than 240 000 men largely due to PSA screening. Recently a federal task force found that PSA screening led to the over detection and overtreatment of prostate cancer and recommended against its use.[8] A chemoprevention strategy that reduced a significant number of low-grade prostate cancers could have an indirect effect on the overtreatment problem. We note that active surveillance continues to be underutilized, and radical treatments overutilized, for low risk prostate cancer patients both in the United States and many other countries.

In 2011 the FDA recommended against the use of 5ARIs for chemoprevention, citing the increased risk of high-grade tumors and a change in the label for these agents finasteride was required.[9] The specter of higher death rates for 5ARI treated patients was raised. The recent PCPT report clearly demonstrates no differences in survival with up to 18 years of follow-up.

Despite the merits of this study and the clear demonstration that 5ARIs can reduce

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the risk of Gleason 2–6 prostate cancer, this study in not without flaws. It is has never been apparent to these authors why the PCPT report chose to group Gleason 7, 8, 9 and 10 together as high-grade cancer; more common convention would be to group Gleason 8, 9 and 10 together as high-grade. Prostate cancer that was diagnosed after 2004 may not have been fully captured. The current study presents no data on prostate cancer treatment which may vary widely and influence outcome. Additionally the authors report an overall survival, but could not report on cancer specific survival because much of the data was abstracted from the social security death index which does not record this information.

Dutasteride is a 5ARI that inhibits both the type I and II 5ARI. Similar to the PCPT with finasteride, a randomized trial was performed with dutasteride, which demonstrated a reduction in the incidence of Gleason 2–6 cancers in men with an elevated PSA, but a prior negative biopsy compared with placebo.[10] Over a full 4 years of study no differences were noted in Gleason 7–10 cancers. Although the numbers of tumors with Gleason scores of 8–10 were similar in the two groups during years 1 and 2 and during years 3 and 4; there were significantly more tumors with Gleason scores of 8 to 10 in the dutasteride group as compared with placebo group. For those who believe in induction of higher grade cancers by 5ARIs, these data were worrisome.

In summary, while 5ARIs have clearly demonstrated to reduce the risk of developing low risk prostate cancer, existing data also demonstrates the possibility of higher grade tumors. For those who are supporters of 5ARIs, the recent PCPT update offers reassurance that finasteride use not associated with an increased risk of mortality with up to 18 years of follow-up. On the other hand, finasteride use was not associated with any reduction in mortality either. It is most likely that the cancers prevented by 5ARIs are the same ones that should be surveilled if detected.

AUTHOR CONTRIBUTIONS

All authors were responsible for the overall study design and content and contributed significantly to the manuscript and approved the final version.

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